

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 0501-PCT-5	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2004/017456	International filing date (<i>day/month/year</i>) 28 May 2004 (28.05.2004)	Priority date (<i>day/month/year</i>) 30 May 2003 (30.05.2003)]
International Patent Classification (IPC) or national classification and IPC A61K 38/00		
Applicant AMYLIN PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).
 2. This REPORT consists of a total of 6 sheets, including this cover sheet.
- In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

<input checked="" type="checkbox"/>	Box No. I	Basis of the report
<input type="checkbox"/>	Box No. II	Priority
<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input checked="" type="checkbox"/>	Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/>	Box No. VI	Certain documents cited
<input type="checkbox"/>	Box No. VII	Certain defects in the international application
<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report 01 December 2005 (01.12.2005)
Facsimile No. +41 22 740 14 35	Authorized officer <div style="text-align: center; font-weight: bold; margin: 10px 0;">Masashi Honda</div> Telephone No. +41 22 338 70 10

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 29 AUG 2005

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
DAVID R. MARSH, PH.D.
ARNOLD & PORTER
555 TWELFTH STREET, NW.
WASHINGTON, DC 20004-1206

Date of mailing
(day/month/year) **26 AUG 2003**

Applicant's or agent's file reference

FOR FURTHER ACTION

See paragraph 2 below

0501-PCT-5

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US04/17456

28 May 2004 (28.05.2004)

30 May 2003 (30.05.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 38/00 and US Cl.: 514/7

Applicant

AMYLIN PHARMQCEUTICAL, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Jennifer Ione Harle

Telephone No. (571) 272-1600

Form PCT/ISA/237 (cover sheet) (January 2004)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/17456

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/17456

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
- ☐ paid additional fees
- ☒ paid additional fees under protest
- ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
- ☒ not complied with for the following reasons:
- See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-3, 4 (in part), 6, 7 (in part), 8, 9 (in part), 10 (in part), 15-26 and 44

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/17456

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>Please See Continuation Sheet</u>	NO
Inventive step (IS)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>Please See Continuation Sheet</u>	NO
Industrial applicability (IA)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>Please See Continuation Sheet</u>	NO

2. Citations and explanations:

Claims 1-3, 4 (in part), 6, 7 (in part), 8, 9 (in part), 10 (in part), 15-26 and 44 meet the criteria set out in PCT Article 33(2), because the prior art does not teach the combination of a extendin-4, polyarginine, and acetic acid, where pH of the composition and the acetic acid does not cause precipitation of the polyarginine and has a mono-anionic or neutral net charge.

Claims 1-3, 4 (in part), 6, 7 (in part), 8, 9 (in part), 10 (in part), 15-26 and 44 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Young discloses a pharmaceutical composition and method for using extendin-4 for transmucosal administration using an acetate/glutamate buffer/ (comprises acetic acid/glutamic acid), with a pH in the range of 3-7 and further ingredients including mannitol, m-cresol, methylcellulose and other excipients as needed, i.e. bioadhesive agents are well-known additional excipients in the art and carbomer and polycarbophil are two very well known bioadhesive agents used. As per the amounts of the components it is routine in the art to optimize components dependant upon the specific use and reagents. Abstract, pg. 12, lines 17-20, pp. 12-13, lines 21-5, pp. 13-14, lines, 19-4, pp. 16-21, pp. 23-24, pp. 32-33, pp. 51-53, 56-69-70. Moreover, most of the ranges taught by Young overlap those claimed and thus optimization would be even more routine to ensure compatibility with the polyarginine. Pp. 13-14, lines, 19-4, pp. 16-21, pp. 23-24, 56-70. Young does not disclose the use of polyarginine, however, he does disclose the need to find better transmucosal routes of administration because the properties of peptides and proteins make them difficult to utilize. See pp. 12-13. Ryser discloses that cationic polypeptides and in particular polyarginine effect or enhance cellular uptake of molecules which are either excluded from or are poorly taken up by cells, i.e. the same problems set forth by Young, for some proteins as much as by a factor of several hundred fold and dramatically increases cellular transport of molecules such as drugs co-factors nucleotides nucleotide analogs - gaining a very important advantage by using selected cationic polymers, such as poly-L-lysine and poly-L-arginine, which are excellent substrates for physiologic proteolytic enzymes present in mammalian cells, i.e. after having served as a transport carrier, they can be digested or otherwise broken down inside the cells into normal physiologic by-products. Cols. 3-4. Ryser further discloses that there are a wide variety of molecules which can be covalently bonded to cationic polymers including, peptides and that typically the positively charged groups are primary, secondary or tertiary amines which ionize at or around neutral pH, i.e. the range claimed to prevent precipitation, and that cationic poly(amino acids are preferred because of the outstanding enhancement in cellular uptake which they provide along with the digestion by proeolytic enzyme some poly(amino acids), i.e. polyarginine, provide. Cols. 5-6. Moreover, Ryser discloses that polycationic amino acids have multiple uses including chemotherapeutic applications antimicrobial applications genetic diseases, storage diseases, enhancing cellular uptake of polypeptide hormones such as insulin, cellular transport for other molecules having biological functions, i.e. extendin-4 - which as taught by applicant treats diabetes and lowers plasma glucose or delays and or slows gastric emptying or inhibiting food intake. Cols. 15-16. Thus it would have been obvious to utilize polyarginine with the combinations in Young for the express benefits taught by Ryser and to negate the problems set for in Young.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/17456

Supplemental Box
In case the space in any of the preceding boxes is not sufficient:

V.1. Reasoned Statements:

The opinion as to Novelty was positive (Yes) with respect to claims 1-3, 4 (in part), 6, 7 (in part), 8, 9 (in part), 10 (in part), 15-26, and 44

The opinion as to Novelty was negative (No) with respect to claims NONE

The opinion as to Inventive Step was positive (Yes) with respect to claims NONE

The opinion as to Inventive Step was negative (NO) with respect to claims 1-3, 4 (in part), 6, 7 (in part), 8, 9 (in part), 10 (in part), 15-26, and 44

The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-3, 4 (in part), 6, 7 (in part), 8, 9 (in part), 10 (in part), 15-26, and 44

The opinion as to Industrial Applicability was negative (NO) with respect to claims NONE